REMARKS

This is in response to the Official Action mailed March 28, 2002 for the above-captioned application. Reconsideration of the application in view of the remarks herein is respectfully requested.

Applicants request an extension of time sufficient to make this response timely, and enclose the appropriate fee. The Commissioner is authorized to charge any additional fees or credit any overpayment to Deposit Account No. 15-0610.

While Applicants do not concede the merits of the Examiner's rejection, claims 4 and 15 which were rejected under 35 USC § 112, first paragraph have been cancelled.

The Examiner rejected claims 6, 11, 17 and 21 under 35 USC § 112, second paragraph. Claims 6 and 17 has been amended to remove the grammatical error. With respect to the remainder of the rejection, however, Applicants point out that so-called Markush language is only "one acceptable form" for expressing an alternative expression in a claim. (MPEP § 2173.05(h).) To support a rejection for indefiniteness, the Examiner must indicate why a person skilled in the art would not understand the scope of the claim, not merely state that it does not follow a specific format. The Examiner has not done that here. Further, Applicants do not perceive any ambiguity. The composition of claim 1 recites a cationic lipid. Claims 6 and 17 recite a list of cationic lipids, and say that the cationic lipid is a lipid selected from this list. Claims 11 and 21 provide similar lists from which the antigenic molecule is selected. Thus, Applicants respectfully traverse the remainder of the rejection and request that the rejection be withdrawn or clarified.

The Examiner appears to state that the claims are not entitled to the benefit under 35 USC § 120 of the filing date of the earlier applications referenced in the application, but seems to be making a comparison of the specifications of the two applications rather than the claims. Specifically, the Examiner states that the parent application, 09/078,954, "does not provide written support for the utility of any composition comprising a nucleic acid polymer and any cationic lipid within the context of immune-adjuvant for inducing an useful immune

response against any desire molecule." It is noted, however, that claim 1 is directed to "an immunostimulatory composition" and that beyond this preamble statement of the type of composition, there is no recitation of intended use. Compositions which fall within the scope of the claims now presented are clearly found in the parent application. Thus, Applicants submit that the properties of these compositions (i.e., that they act as non-sequence specific immune stimulators) are inherent, and that the addition of a description of these inherent properties does not deprive the claims of the benefit of the priority date. In this regard, Applicants note that the Examiner has relied on this same inherency as a basis for justifying the rejection based on the art. Furthermore, Applicants note that the parent case teaches an increase in clearance rate when liposomes with oligonucleotide are administered in repeat doses, but no when empty liposomes are used. (Example 4.9, Fig. 17) This can only be ascribed to the induction of an immune response. Thus, the application does contain support for the compositions of the invention having immunostimulatory properties. Accordingly, Applicants request reconsideration of the Examiner's statement regarding priority.

The present invention is based on the surprising discovery that compositions comprising nucleic acid polymers **encapsulated** in a lipid particle comprising a cationic lipid act as immunostimulatory molecules in a non-sequence-specific way. This immunostimulation is not just based on any inherent immunostimulatory characteristics of the lipid particle and occurs even when the oligonucleotide is not itself effective to cause immunostimulation. Thus, the particles display a wholly unrecognized and unexpected synergistic activity.

On the merits, the Examiner rejected claims 1-2, 6 and 20 under 35 USC § 102 as anticipated by Felgner et al (US Patent No. 5,703,055), relying further on Bei et al. for a teaching of properties allegedly inherent in the Felgner compositions. The Examiner characterizes the present invention very broadly, and ignores many of the limitations in the claim. Claim 1 is directed to a composition (not a method as indicated by the Examiner). In the composition as claimed, the nucleic acid polymer is **encapsulated** in a lipid particle. Felgner does not disclose such a structure. Rather, Felgner describes complexes in which the DNA is not encapsulated

inside discrete, vesicular particles, but is sandwiched between lipid layers to form irregular, unstable macroscopic DNA/lipid structures. Hope et al. 1998, Mol. Membr. Biol. 15: 1-14 (copy attached). Thus, Felgner does not anticipate any of claims 1, 2, 6 and 20.

Claims 1-3, 6 and 20 stand rejected as anticipated by Friemark et al. or Ishi et al. Applicants note that these references are not available as prior art if the priority of the parent application is correctly afforded the present claims. Furthermore, Applicants respectfully point out that there is no basis in these references to support the conclusion that they disclose "identical compositions" to those now claimed. As noted above, the present invention claims compositions in which the nucleic acids are "encapsulated." Friemark teaches plasmid:cationic lipid **complexes**. In Ishii, the DNA and the cationic liposomes are merely mixed together, and thus there is no indication of encapsulation. Thus, the rejected claims all of which require encapsulation, are not anticipated by the documents, even if they are properly considered as prior art.

The Examiner also rejected claims 1-3, 5, 9-14, 16, 20 and 21 as anticipated by Krieg et al. While the text of the '646 patent at Col. 12, line 27 mentions DNA "encapsulated within" a targeting means, the '646 patent never specifically discloses encapsulation of DNA in a cationic lipid-containing lipid particle, nor does it teach how such encapsulation would be accomplished. Applicants therefore suggest that the Krieg patent does not anticipate the rejected claims.

The Examiner also rejected claims 1-3, 5-14 and 16-21 are obvious over Felgner, Freimark and Ishii, taken with either Meers or Wheeler, and acknowledged prior art. The secondary references are cited to address additional components recited in dependent claims. Without conceding the accuracy of the Examiner's assertions concerning the appropriateness of combining these references, Applicants respectfully submit that this rejection is in error based on the Examiner's failure to consider the significance of the term "encapsulated" in the independent claims, and in light of the unexpected properties of the claimed compositions.

The importance of the term "encapsulated" in the claims is discussed above. None of the primary references in this rejection disclose encapsulated (as opposed to merely complexed) DNA, and the Examiner has not indicated why such a change is suggested by the art. Furthermore, as reflected in the examples in the application, the properties of the compositions of the invention are superior, and unexpected. These results can be seen from the Figures in the application. For example, in Fig. 28, secretion levels for various cytokines are shown for free oligonucleotide, empty liposomes, and the composition of the invention. In each case, the empty liposome is inactive and the free oligonucleotide is inactive or only moderately active. The combination of the invention, however, in each case stimulates significant cytokine production. Similar results are seen in other figures in the application. Nothing in the art suggest this result. Felgner says that some nucleotides may produced expressed antigen to produce an antigen-specific response, some reference shows that some lipid particles are imunogenic, but nothing discloses or suggests that polynucleotides encapsulated in cationic lipid particles will result in a synergistic humoral (non-antigen specific) immune response, even when neither the polynucleotide nor the cationic lipid particle is independently effective to produce such a response.

For the foregoing reasons, Applicants submit that all claims are in form for allowance. Favorable reconsideration is respectfully requested.

Respectfully submitted

Marina T. Larson, Ph.D.
Attorney for Applicants
PTO Reg. NO. 32,038

+1 970 468 6600 x 152

MARKED UP COPY OF AMENDED CLAIMS

6. The composition according to claim 1, wherein the cationic lipid is selected from [the] among DODAP, DODMA, DMDMA, DOTAP, DC-Chol and DDAB.

17. The composition according to claim 11, wherein the cationic lipid is selected from [the] among DODAP, DODMA, DMDMA, DOTAP, DC-Chol and DDAB.